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A Mathematical Model of Pancreatic Cancer Growth and Response to Treatment

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A MATHEMATICAL MODEL OF PANCREATIC CANCER GROWTH AND RESPONSE TO TREATMENT

by

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Pancreatic cancer is one of the leading causes of death due to cancer in the United States. Analyzing the effects of radiation is extremely valuable in determining when a patient is allowed surgical resection, which is, presently, the only potentially curative treatment for pancreatic cancer. This study examines pancreatic tumor growth and shrinkage to predict tumor response and change of resectability for pancreatic cancer patients undergoing radiation therapy. This is done using ordinary differential equations as a mathematical model. Mathematical models have increasingly been applied to various biological systems/processes to analyze the principles involved. In our project, a population dynamical model is used along with suitable assumptions to study the tumor growth, and the model parameters are carefully calculated from references. To model the tumor response under radiotherapy treatment, a linear-quadratic (LQ) model is incorporated with the tumor growth model. The coupled model is used to observe the mechanisms involved in pancreatic cancer growth and radioresistance. Numerical analysis of the model takes place using modeling software (MATLAB). We found that the implementation of higher doses of radiation in a smaller amount of fractions more effectively decreases the cancer cell size with and without a radioresistance factor.

Keywords: mathematics, applied mathematics, mathematical biology, mathematical modeling

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Table of Contents

Chapter 1

Introduction

Pancreatic cancer is one of the leading causes of death due to cancer in the United States. This is due to the late diagnosis of the disease. Presently, the only potentially curative treatment for pancreatic cancer is surgical resection. Radiotherapy and/or chemotherapy are the most common treatments to decrease the tumor size before surgery. Therefore, more research needs to be done on the dynamics of pancreatic cancer to predict response to treatments of radiotherapy.

Pancreatic cancer contains cancer stem cells (CSCs) which are stem-like cells that exhibit extreme proliferative potential [15]. Along with CSCs, there are progenitor and differentiated cancer cells (DCCs). CSCs produce progenitor cells upon division. Similarly, progenitor cells create DCCs. The division is classified into two types: symmetric and asymmetric (Figure 1.1). CSCs can produce progenitor cells, asymmetrically, by producing one CSC and one progenitor cell. An equivalent incident happens with progenitor cells when dividing. Symmetric division, in which division results in two identical cells, was proven to result in equivalent conclusions when modeling growth [4]. In addition, cancer stem cells make up a small subpopulation of the tumor and are more radioresistant than other types of cancer cells.

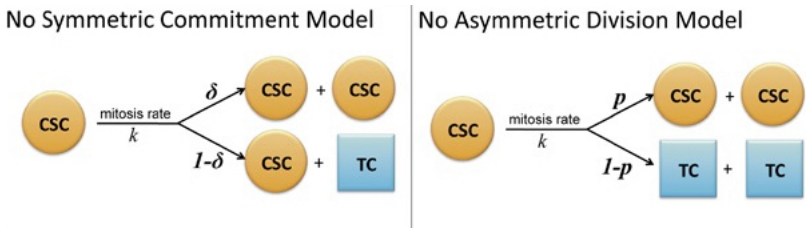

Figure 1.1: Model of Asymmetric and Symmetric division. TC are other tumor cells. Cell division is modeled via the no asymmetric division model in this paper. Adapted from [4].

The most common radiotherapy treatments are Stereotactic body radiotherapy (SBRT) and conventionally fractionated radiotherapy (CFRT) [11, 17]. SBRT performs higher doses in a smaller amount of fractions while CFRT performs lower doses in a larger amount of fractions. Radiotherapy treatments need to take the dynamic nature of cancer into account. Potential treatments should limit the tumor size, but also focus on the most resistant cancer cells.

Mathematical models have increasingly been applied to various biological systems/processes to analyze the principles involved. They have been used extensively in cancer models in response to treatment [1, 4, 16]. However, there is limited research in pancreatic cancer as it is incredibly variable from patient to patient. Despite this, there have been mathematical models developed for prognosis, detection of biomarkers, metastasis, and treatment with chemotherapy [3, 7, 8, 14].

This study examines pancreatic tumor growth and shrinkage to predict tumor response and change of resectability for pancreatic cancer patients undergoing radiation therapy. This is done using differential equations as a mathematical growth model and a widely used equation to represent the effect of radiotherapy, the Linear Quadratic Model. We show that SBRT is more effective at reducing the end tumor size compared to CFRT with and without an added resistance factor of cancer stem cells. Further, we demonstrate that higher dose per fraction treatment regimens in

shorter periods of time result in smaller tumor sizes.

Chapter 2

Methods

In this section, we first introduce a three-compartmental cancer growth model to explain the dynamics of pancreatic cancer growth. Then, the Linear-Quadratic (LQ) model is incorporated to study how cancer cells respond to radiotherapy.

2.1 Three-Compartmental Cancer Growth Model

There are three types of cancer cells to study: cancer stem cells (represented as C_0), progenitor cells (C_1), and differentiated cancer cells (C_2). We model the growth through symmetric division where CSCs produce two progenitor cells or two CSCs upon division (Figure 2.1). An equivalent incident happens with progenitor cells when dividing.

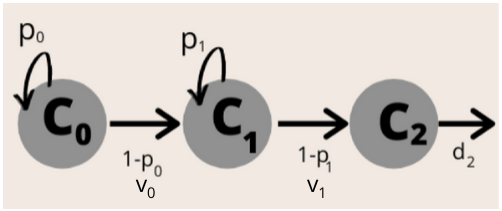

Figure 2.1: Cancer Cell Hierarchical Model

P_0 is the probability for cancer stem cells to self-renew upon division while $1 - P_0$ is the probability of symmetric differentiation to yield two progenitor cells. P_1 is the

probability for progenitor cells to remain as progenitor upon division while $1 - P_1$ is the probability of becoming differentiated cells after division. d_2 is the rate at which differentiated cancer cells are removed from the system, which may occur through natural cell death; while the death rate of CSCs and progenitor cells is set to 0, assuming that they have unlimited replicative potential. v_0 and v_1 are proliferation rates of cancer stem cells and progenitor cells, respectively.

Below is the system of ordinary differential equations for pancreatic cancer cell growth.

$$\begin{aligned} \frac{dC_0}{dt} &= (2p_0 - 1)v_0C_0 \\ \frac{dC_1}{dt} &= 2(1 - p_0)v_0C_0 + (2p_1 - 1)v_1C_1 \\ \frac{dC_2}{dt} &= 2(1 - p_1)v_1C_1 - d_2C_2 \end{aligned} \tag{2.1}$$

To determine the parameter values, references were explored and evaluated under the model assumptions. A common value for p_0 is 0.505 [16]. P_1 was determined by sensitivity analysis to provide a ratio of CSCs that correlated with literature (Details in Section 3.1). According to data from pancreatic cancer studies [3, 14], the value of v_0 is between 0.003 to 0.005 day^{-1}. These studies show data on the mean doubling time of the tumor. The rate is defined as

$$\frac{\ln(2)}{T_{pot}}\text{day}^{-1}$$

where T_{pot} is the tumor doubling time in days. The studies show growth of the cancer cells as a whole, so we adopt this number as the growth rate of CSCs, v_0. Sensitivity

analysis was performed for v_1 and d_2, but to allow for simplification, we assume $v_1 = d_2 = v_0$ (Details in Section 3.1).

2.2 Linear-Quadratic Model in Radiotherapy

The LQ model implements the biological effects radiotherapy has on cancer cells to show a survival fraction. It assumes that the radiation dose is enough to quantify the result. This is because an abundance of ionizing particles are shot at the cell in any given dose. The damage caused by this radiation is the most important in the DNA within the cell nucleus. The ionizing particles cause double stranded breaks in the DNA in which most are repaired quickly. However, some are misrepaired via an interaction between two double stranded breaks. It is determined that within several units of radiation (unit:Gy) at least one misrepair takes place. In addition to the double stranded breaks, other random lethal lesions can also take place in the DNA. Both of these results cause cell death. An assumption of the LQ model is that stochastic fluctuations are negligible or Poisson distributions hold for the number of double stranded breaks per cell and cells per population. The LQ model holds for times greater than the radiation end time and large compared to the repair time constant. Below is the LQ model for one compartment, where α and β describe radiobiological parameters of the cell, SF is the surviving fraction and D is the accumulated dose in Gy.

$$SF(D) = e^{-\alpha D - \beta D^2} \tag{2.2}$$

The LQ model is considered to be a quantitative model of cell survival after radiation and it is influenced by the following factors: Intrinsic tissue radio-sensitivity (α, β) and dose/fractionation. The first term in the exponent refers to unrepairable

lethal lesions and the second term refers to double stranded breaks that cannot be repaired. α and β depend on the type of cancer. The α/β ratio is a quantitative factor for various responding tissues. α is the coefficient of the linear term of the exponent and β is the quadratic term. Many sources document the α value near 0.02 Gy^{-1} and an α/β ratio of 10 Gy ($\pm$5 Gy) for pancreatic cancer [10, 13].

A three-compartment linear quadratic model similar to Sheng and colleagues [16] is used to model the treatment effect on three cell types. To analyze the effect of tissue sensitivity, we assume the three cell types have different sensitivity parameters. β is assumed to be zero for DCCs as they don't divide. Therefore, radiation affects these cells linearly [5, 9].

The LQ model is implemented discretely with the growth model throughout treatment. Specifically, the LQ model is performed on the growth equations daily, with exception of weekends. For CFRT, the simulation is run for 38 days including weekends and for SBRT, it is run for only 5 days.

A similar effect can be observed when using a continuous model with a differential equation: $\frac{dN}{dt} = (-\alpha D - \beta D^2)N$ and therefore $N = N_0 e^{(-\alpha D - \beta D^2)t}$ for a single-fraction treatment.

Chapter 3

Results

In this section, we first conduct a sensitivity analysis of the pancreatic cancer growth model to explore the feasible range of the parameters. Secondly, the LQ model is analyzed to observe the effects with respect to different levels of resistances and/or doses. Then, the coupled model consisting of the growth model and LQ model is simulated to determine the effectiveness of SBRT and CFRT with and without a resistance factor of CSCs. Finally, hypothetical treatments are proposed in order to observe a trend in the dose per fraction and effectiveness.

3.1 Sensitivity Analysis of Parameters in the Growth Model

To explore the feasible range of parameter values, we first analyze the steady states and the sensitivity of the growth model. For the system to achieve a steady state, the requirement $p_0 \to 1/2$ as $t \to \infty$ must be maintained to prevent exponential growth or the extinguishment of the stem cell population and the tissue as a whole. When $p_0 > 1/2$, $\frac{dC_0}{dt}$ is positive, so growth of the stem cells occurs. On the other hand, when $p_0 < 1/2$, $\frac{dC_0}{dt}$ is negative, so the stem cells shrink in size. Our study is primarily focused on development of pancreatic cancer and radiotherapy treatment. In this scenario, the cancer system may not reach a steady state, and growth of

the stem cells occurs. As a result, we study the system at a dynamic state after approximately 5 years and take values for p_0 exceeding 1/2.

The requirement $p_1 < 1/2$ as $t \to \infty$ must be maintained to control the growth of the progenitor cells and of the tissue as a whole. When $p_1 > 1/2$, $\frac{dC_1}{dt}$ is always positive, so growth of the progenitor cells occurs regardless of the state of the stem cells. On the other hand, when $p_1 < 1/2$, $\frac{dC_1}{dt}$ is possible to become negative, so the progenitor cells shrink in size. Also, in cancer cell growth, it is feasible to take $p_1 < 1/2$ in order to lead to growth of the tumor.

A sensitivity analysis was performed for p_0, v_0, p_1, v_1, and d_2. All simulations were started with the initial conditions of $C_0 = 1$ and $C_1 = C_2 = 0$ at $t = 0$ as all other cancer cells arise from cancer stem cells. Figure 3.1 shows the dependence of population size of cancer cell types on p_0, v_0, p_1, v_1, and d_2. To make the analysis simple, when not analyzed, the parameters are set to be constants. As shown in Figure 3.1, the number of all cancer cells increase with p_0. Only progenitor cells and differentiated cells increase significantly with p_1, therefore the total cancer cell size increases. There is a dramatic increase in progenitor and differentiated cells while a slight increase in CSC as v_0 increases, leading to an increase in total cancer cell size as well. Increasing v_1 causes different effects on the cell types: an increase in the differentiated cancer cell size, a decrease in the progenitor cell size, and CSC size remains constant as expected, which causes a slight decrease in the total cancer cell size. Finally, with increasing d_2, the only cell type that is affected is differentiated cancer cells, it decreases causing a dramatic reduction in total cancer cell size. From the sensitivity in Figure 3.1, a treatment targeting to shrink the cancer size could focus on decreasing p_0, v_0, p_1 while increasing v_1 and d_2. A treatment targeting to kill the stem cells could focus on decreasing p_0 and v_0, though the effect of a decreasing v_0 is not significant. Also, as the graphs in Figure 3.1 show, the values of d_2 and v_1 do

not affect the cancer stem cell growth greatly. Therefore, to allow for simple analysis, v_1 and d_2 are set to equal v_0 in future simulations.

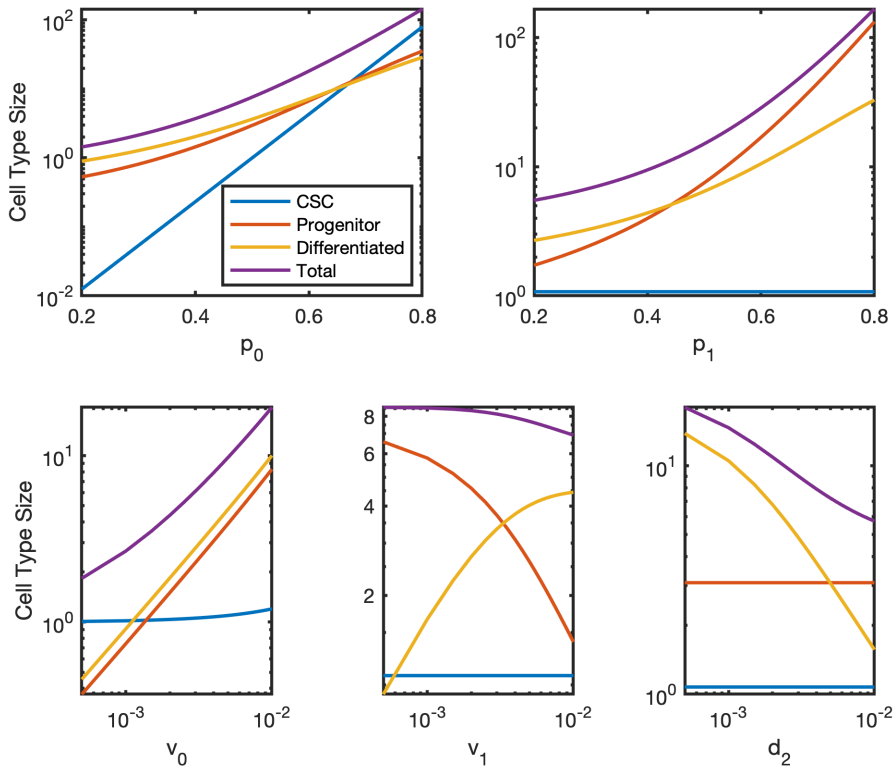

Figure 3.1: Cell Population Sizes. Dependence of cell population sizes of different cancer cell types on p_0, v_0, p_1, v_1, and d_2 at 5 years ($t = 1825$ days). The sizes of the cancer stem cells, progenitor cells, differentiated cancer cells, and total cancer cells are given by C_0, C_1, C_2, and $C_0 + C_1 + C_2$, respectively. Corresponding parameters chosen are: $p_0 = 0.505$, $p_1 = 0.35$, $v_0 = 0.004$, $v_1 = 0.004$, and $d_2 = 0.004$. Initial conditions: $C_0 = 1$ and $C_1 = C_2 = 0$ at $t = 0$.

As cancer stem cells were proliferating, we conducted another analysis focusing on the ratio of stem cells in the tumor. According to Cecconi and colleagues [2], pancreatic cancer stem cells make up less than 1% of all cancer cells in the tumor. The analysis was performed to find an optimal range of parameters that fit this ratio. Figure 3.2 shows the dependence of cancer stem cell ratio on p_0, v_0, p_1, v_1. The

same initial and parameter values were used as in Figure 3.1. As shown in Figure 3.2, the CSC ratio increases with p_0 , v_1, and d_2, and decreases with p_1, v_0. Since stem cells are the source of the tumor, this analysis suggests with increasing p_0, v_1, and d_2 or decreasing p_1 and v_0, the growth of progenitor/DCCs will be in an inactive enlargement stage. Combining the observation in the first sensitivity analysis, an effective treatment would allow for a decrease in v_0 and p_1 and an increase in v_1 and d_2. However, the result of a decreasing p_0 is versatile.

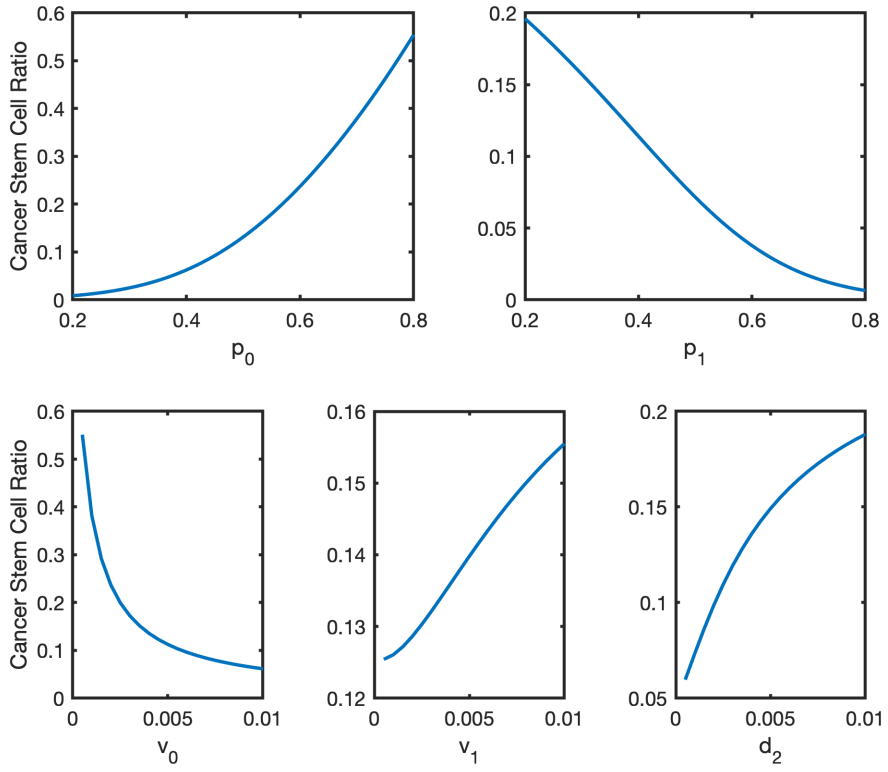

Figure 3.2: Cancer Stem Cell Ratio. Dependence of the cancer stem cell ratio on p_0, v_0, p_1, v_1, and d_2 at 5 years ($t = 1825$ days). The ratio is given by $\frac{C_0}{(C_0+C_1+C_2)}$. Corresponding parameters chosen are: $p_0 = 0.505$, $p_1 = 0.35$, $v_0 = 0.004$, $v_1 = 0.004$, and $d_2 = 0.004$. Initial conditions: $C_0 = 1$ and $C_1 = C_2 = 0$ at $t = 0$.

Continuing parameter exploration, we performed a steady-state analysis of the ratio of CSCs. To account for a near-steady state, a threshold was used to ensure

that the near-steady states are reached in simulations when there was only a 1% change in ratio percentage over time. To fit with our model assumptions of p_1 being less than 0.5, the p_1 range was kept from 0.2 to 0.5. The parameter, p_0 was fixed at 0.505 throughout the analysis to agree with the dynamic nature of stem cells as noted earlier. The parameters, v_0, v_1, and d_2, took the values of 0.002 to 0.008. The end time was set to 5 years, but the simulation stopped when a steady state was reached. The simulation results show that steady states were obtained when p_1 was less than 0.3, while the values of v_0, v_1, and d_2 were more flexible. These steady states ended in a ratio of CSCs of around 24% with the lowest at 12%, which suggests the cancer is not actively developing at these parameter values. However, these simulations were stopped when a near-steady state was reached (1% change in ratio percentage), so if the simulation ran for the full 5 years, the ratios would decrease. From this data, it is clear that p_1 needs to be greater than 0.3 in order to allow for active development of the cancer allowing the ratio of progenitor cells and DCCs to increase.

To analyze when the ratio of CSCs would end in 1%, the range of p_1 is sampled from 0.55 to 0.8, which indicates the progenitor cell mainly conducts symmetric divisions to renew itself and would significantly increase the population of progenitor cells. The other parameters were kept the same as in the previous simulations. With these values, ratios of CSC less than 0.9% could be reached when p_1 was more than 0.55. However, v_0, v_1, and d_2 did not affect the end ratio greatly and could take values from 0.002 to 0.008 and still result in a low ratio. A majority of the runs that resulted in a ratio less than 0.5% ended in a near-steady state within the full 5 years. The ratio of CSCs being less than 1% shows that with progenitor cells conducting active self renewal, the cancer is developing rapidly (by producing more progenitor cells).

3.2 Sensitivity Analysis of Radiation Parameters in LQ Model

In LQ model Eqn (2.2), the choices of the sensitivity parameters are critical. It is clear that high α/β ratio will have more flat or nearly-constant rates of cell killing with increasing dose, while low α/β ratios will show a more rapid killing curve with increasing dosage. As shown in Figure 3.3, the simulations are conducted with a single dose of radiation.

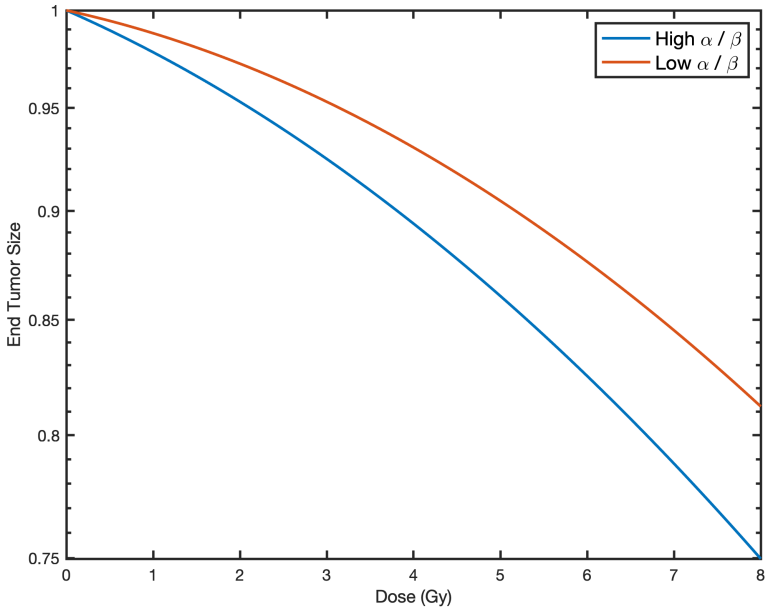

Figure 3.3: Surviving Fraction after a Single Dose of Radiation. Dependence of end tumor size on dosage for a single dose of radiation. The tumor was described as one entity for simplification. The α for the low ratio was set at 0.01 Gy and 0.02 for the high ratio. β was fixed at 0.002 Gy^{-2}. The initial size of the tumor was set to 1.

Fractional dosage decreases the impact of the quadratic term by lowering the dose per fraction. Therefore, lower α/β ratios will be spared more with fractionation. Eqn (3.1) shows the impact fractionation has as it takes into effect the fractionation scheme on the overall survival where d is the dose per fraction, n is the number of

fractions, and D is the accumulated dose.

$$SF(D) = \left(e^{-\alpha d - \beta d^2}\right)^n = e^{n(-\alpha d - \beta d^2)} = e^{-D(\alpha + \beta d)} \tag{3.1}$$

A good treatment plan seeks a balance between fractionation and dose in order to decrease the amount of sparing that is seen in tissues with low α/β ratios while decreasing cell survival of all cancer cell types.

Figure 3.4 shows the difference between the effect of dosage on high and low α/β ratios in a 28 fraction treatment and a 5 fraction treatment. Each treatment had the same accumulated dose (D), represented on the x axis. Thus the only quantity that changed was the number of fractions, n, and the dose per fraction, d, needed to reach the accumulated dose. As expected, the higher fraction treatment results in low survival fractions and the low α/β ratios show more resistance. Along with this, the 5 fraction treatment is not as sensitive to the low α/β ratio as the 28 fraction treatment. In addition, the 5 fraction treatment results in more rapid killing curves with increasing dosage. This corresponds with the equation as in the lower fraction treatment, a larger dose per fraction, d, is used.

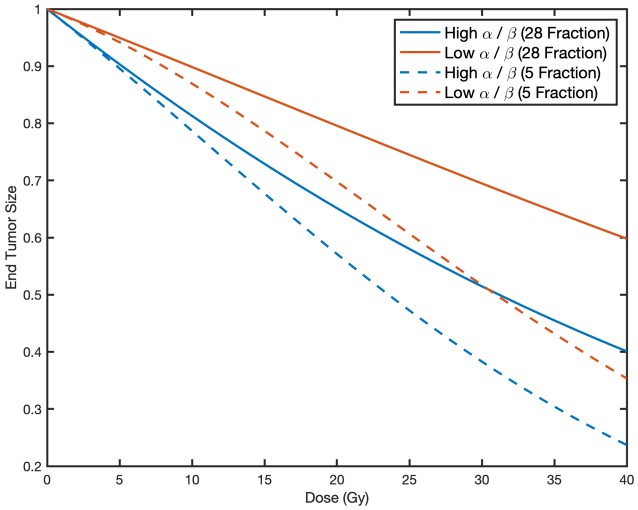

Figure 3.4: End Tumor Size after Fractionated Radiotherapy. Dependence of end tumor size on dose for different fractions of treatment. The tumor was described as one entity for simplification. The α for the low ratio was set at 0.01 Gy and 0.02 for the high ratio. β was fixed at 0.002 Gy^{-2}.The initial size of the tumor was set to 1.

As seen in Figure 3.4, the dose/fraction in the treatment plan is a significant factor. To propose a good treatment plan, we first compare the two commonly used clinical treatment plans: SBRT and conventionally fractionated radiotherapy.

For the first set of results, both treatments were simulated with the same α and β and the same cumulative dosage D. For SBRT 8 Gy was given for 5 fractions for a total of 40 Gy and for conventionally fractionated radiotherapy (CFRT) 1.4 Gy was given for 28 fractions for a total of 40 Gy. In both therapies, the treatment was only done on weekdays allowing time for patient recovery on the weekends. As references before noted that an α/β ratio of about 10 Gy was found for pancreatic cancer, our simulation implemented a ratio range of 0.05 to 25 Gy. This allowed α to range from 0.0001 to 0.05 Gy^{-1} and β to be fixed at 0.002 Gy^{-2}.

Figure 3.5 shows that for both types of therapy the end tumor size decreases with the α/β ratio. Since CFRT has a lower dose per fraction, d, and a larger amount of

fractions, n, it is clear from Eqn 3.1 that the β term is not as large when compared with SBRT. Therefore, there is not as much cell killing in CFRT. As 10 Gy ($\pm$5 Gy) is the common ratio used in references as noted earlier, the size at this ratio can indicate which treatment is more effective. SBRT leads to an end tumor size of about 0.25 at a ratio of 10 Gy while conventionally fractionated radiotherapy ends with a tumor size of 0.3 at this ratio. Therefore, SBRT is more efficient for pancreatic cancer in these simulations with the LQ model only.

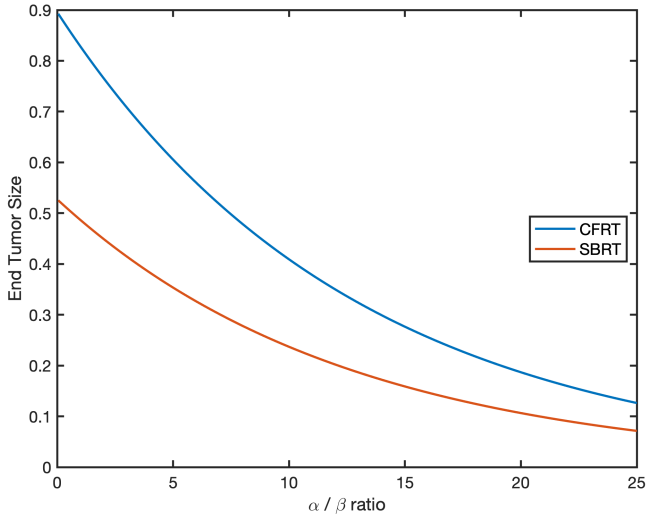

Figure 3.5: LQ Model Simulation with SBRT and Conventionally Fractionated Radiotherapy. Dependence of end tumor size on α and β at the end of treatment. The tumor was described as one entity for simplification. α ranged from 0.0001 to 0.05 Gy^{-1} and β was fixed at 0.002 Gy^{-2}. The initial size of the tumor was set to 1.

3.3 Sensitivity Analysis of Radiation Parameters in Coupled Model

For the sensitivity parameter choice in the three-compartment LQ model, as noted in the methods section, α and β are different for different cell types to reflect their various sensitivity and β is set to zero for differentiated cancer cells as they do not

divide. For simplicity, when we refer to α/β ratio, for DCCs is referring to an that ranges from 0.0001 to 0.05 Gy^{-1} and the potential ratio if there was a β of 0.002 Gy^{-2}.

As in the earlier sensitivity analysis with the LQ model only, α ranged from 0.0001 to 0.05 Gy^{-1} for all cancer cell types and β was fixed at 0.002 Gy^{-2} for CSCs and DCCs (β is zero for DCCs). This allowed for α/β ratios to range from 0.05 to 25 Gy. Also, as in Figure 3.5, SBRT and conventionally fractionated radiotherapy were performed. Initial conditions were taken from Section 3.1 simulations at 2 years when $p_0 = 0.505$, $p_1 = 0.35$, $v_0 = 0.004$, $v_1 = 0.004$, and $d_2 = 0.004$ ($C_0 = 0.2124$, $C_1 = 0.4039$, and $C_2 = 0.3837$ at $t = 0$).

First, we assume CSCs do not have resistance against radiotherapy. In order to analyze the sensitivity of the α/β ratio in the coupled model, simulations were done on a model that assumed equivalent α/β ratios for all cancer cell types (Figure 3.6 Left). In general, as the α/β ratio increases, the cancer cells decrease. For small α/β ratios, SBRT results in lower cancer cells at the end of treatment as the progenitor and CSCs are smaller in size for these small ratios in SBRT. The sparing effect can be seen when comparing the two treatment types at low α/β ratios. Since SBRT implements a higher dose per fraction, the surviving fraction is lower at these small α/β ratios. However, as the α/β ratios increase, corresponding to the more single hit kills, the difference in the surviving fraction becomes smaller between the treatments. Also, for conventionally fractionated radiotherapy, there is a small gap between the effect of the changing α/β ratio on DCCs and progenitor cells. However, for SBRT, there is a large gap between the effect. Therefore, for SBRT, the radiation parameters affect the DCCs and progenitor cells a little differently than in conventionally fractionated radiotherapy.

Next, we assume different radiation sensitivity parameters between the cancer cell

types. It has been shown that cancer stem cells of different cancer cell types [12, 16] are more radioresistant, thereby resulting in lower α/β ratios Therefore, we assumed that progenitor and DCCs would have the same α/β ratios whereas CSCs would have smaller ones. CSCs were assumed to have a resistance factor of 0.5 to lower their α/β ratio (lower single hit kills) that was constant throughout the simulation. Figure 3.6 (middle) shows that with this resistance factor, the surviving fraction of all cell types for SBRT is lower than that of CFRT at low and high α/β ratios which is what was seen in simulations with no resistance factor. These similarities between the simulations with and without the resistance factor show that the added resistance of CSCs does not change the trends seen when comparing both treatments.

Comparing the treatments with and without the resistance factor for CSCs (Figure 3.6, right), a difference can be seen at higher α/β ratios. The amount of DCCs and progenitor cells do not change significantly with and without the resistance factor for CSCs. CFRT is more sensitive to this resistance, while SBRT is not as affected, although there is still some change. In all, comparing the two treatments with the resistance factor, it is clear that SBRT can accommodate this resistance more.

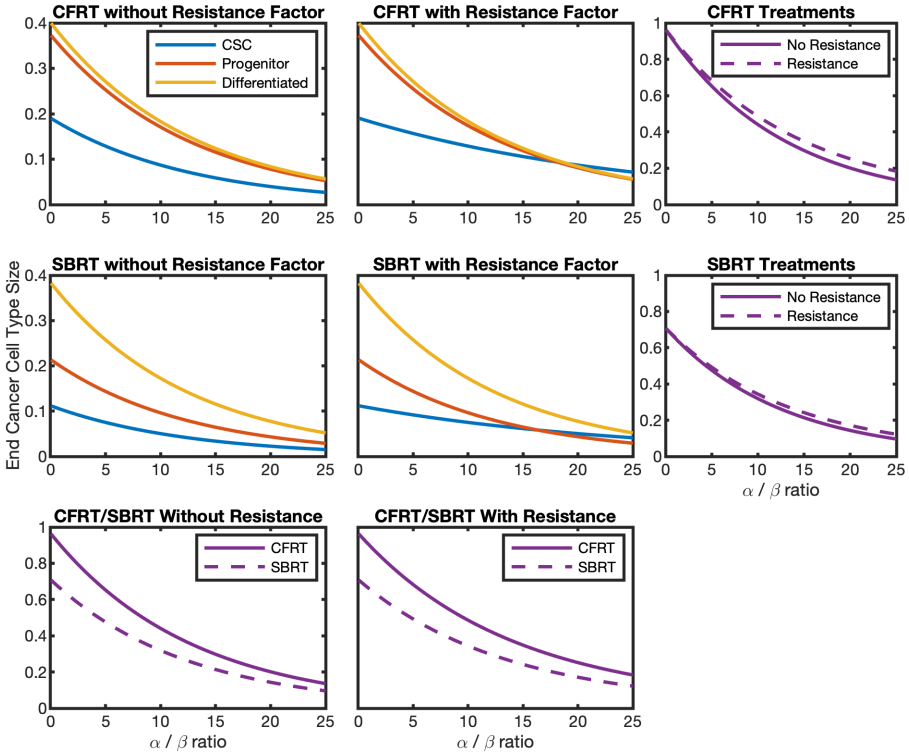

Figure 3.6: Coupled Model Cancer Cell Sizes with Common Treatments. Dependence of end Cancer Cell Type Size on α and β at the end of treatment. The resistance factor for cancer stem cells was set at 0.5 for figures on the right. Note that β is zero for Differentiated Cancer Cells. However, to make the figure simpler, a ratio was used for the axis label even though there is no ratio for DCCs. Initial conditions: $C_0 = 0.2124$, $C_1 = 0.4039$, and $C_2 = 0.3837$ at $t = 0$. Corresponding growth parameters chosen were: $p_0 = 0.505$, $p_1 = 0.35$, $v_0 = 0.004$, $v_1 = 0.004$, and $d_2 = 0.004$. All initial sizes were based on the simulations with the growth model at year two.

3.4 Hypothetical Treatment Plans

As references before noted that an α/β ratio of 10 Gy ($\pm$5 Gy) was found for pancreatic cancer, it is important to find a treatment plan that limits the sparing effect found in CSCs while decreasing the overall tumor ratio. SBRT and conventionally fractionated therapy are the most common radiotherapy methods used in treatment.

However, there are many different variations that can be implemented. Therefore, in this next simulation, the following treatments are analyzed in addition to SBRT and CFRT: 40 Gy given in 3 fractions of 13.3 Gy (high dose per fraction), 40 Gy given in 15 fractions of 2.6 Gy (medium dose per fraction), and 40 Gy given in 40 fractions of 1 Gy (low dose per fraction).

Figure 3.7 shows the sensitivity of the treatments to the α/β ratios with and without a resistance factor. The high dose per fraction treatment shows the most promising results as it is the least affected by the added resistance. The low dose per fraction has very similar results to CFRT in that it is affected more by resistance. From this simulation, it is seen that the higher dose per fraction treatments lead to least amount of cancer cells at the end of therapy. However, the surrounding tissue needs to be taken into account. The radiotherapy treatment needs to be a compromise between sparing healthy cells while killing cancer cells.

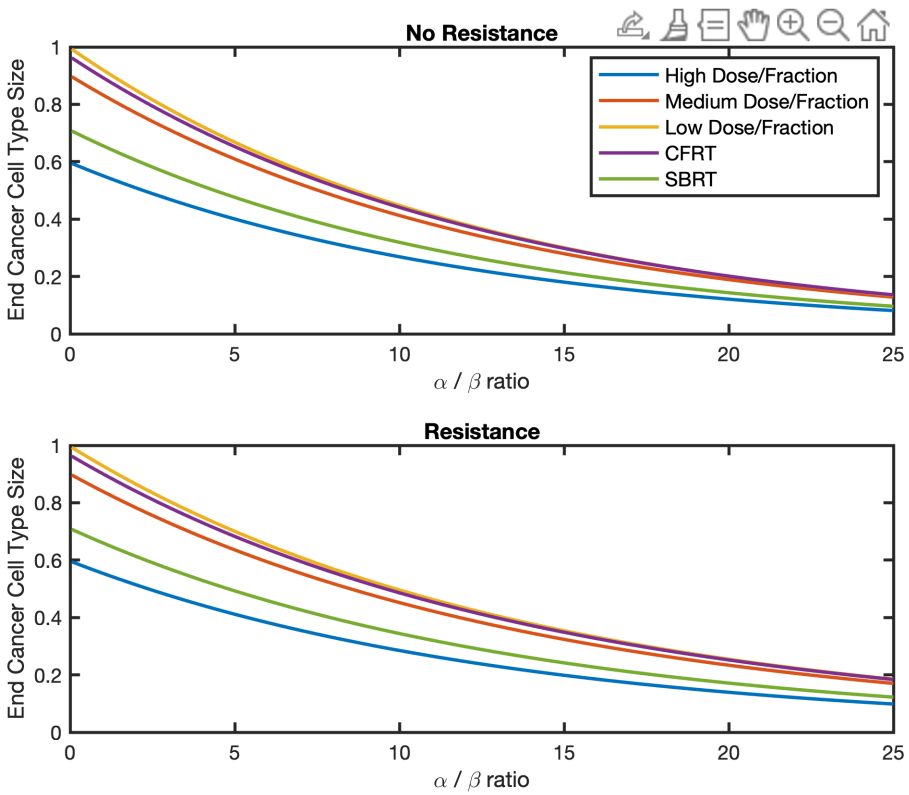

Figure 3.7: Hypothetical Treatments Compared to SBRT and CFRT. Dependence of end Cancer Cell Type Size on α and β at the end of a hypothetical treatment treatment. The resistance factor for cancer stem cells was set at 0.5 for figures on the right. Note that β is zero for Differentiated Cancer Cells. However, to make the figure simpler, a ratio was used for the axis label even though there is no ratio for DCCs. Initial conditions: $C_0 = 0.2124$, $C_1 = 0.4039$, and $C_2 = 0.3837$ at $t = 0$. Corresponding growth parameters chosen were: $p_0 = 0.505$, $p_1 = 0.35$, $v_0 = 0.004$, $v_1 = 0.004$, and $d_2 = 0.004$. All initial sizes were based on the simulations with the growth model at year two.

Chapter 4

Discussion

Our model of pancreatic cancer growth is based on the hierarchy of cells present in a tumor: Cancer Stem Cells, Progenitor Cells, and Differentiated Cancer Cells. The model considers the asymmetric division of CSCs and progenitor cells. Our results on this growth model show that future treatments can focus on decreasing the growth rate of CSCs and the probability of self renewal for progenitor cells while increasing the growth and death rates of progenitor cells and DCCs, respectively. In addition, the probability of self renewal for progenitor cells needs to be greater than 0.3 in order to allow for active development of the cancer allowing the ratio of progenitor cells and DCCs to increase.

The LQ model was used to implement the effect of radiotherapy on cancer cells. This model has radiation parameters, α and β where the latter corresponds to double stranded breaks in DNA and α relies on the single-hit lesions in DNA caused by radiation. Low α/β result from more resistance to radiation. In addition to the radiation parameters, the fractional dosage is also critical. The impact of this can be seen in the quadratic term of the LQ model where the term decreases with more fractionation (causing more resistance).

The most common radiotherapy treatments for pancreatic cancer are SBRT and CFRT. SBRT performs higher doses in a smaller amount of fractions while CFRT

performs lower doses in a larger amount of fractions. The results of simulations of these treatments with our growth model show that SBRT is the more effective treatment with and without a resistance factor on Cancer Stem Cells. SBRT has a lower sensitivity to the resistance factor. The same effect was seen when simulations implementing SBRT treatment run for the same amount of days as CFRT. In these simulations, SBRT treatment is conducted in the first 5 days, then the simulation continues to capture the growth and recovery until the same endtime of CFRT is reached. As shown in the results, the growth of cancer cells in the difference of end times between the treatments is not significant.

In order to test if a more effective treatment could be developed, we implement radiotherapies that have low, medium, and high doses per fraction compared to CFRT and SBRT. Following the results of CFRT and SBRT, the lower doses per fraction are not as effective as the higher doses per fraction with and without the resistance factor of CSCs. The radiotherapy performing 13.3 Gy in 3 fractions is the most effective.

Our simulations focus on the short-term effects of radiotherapy. Therefore, a future task could be observing the long-term effects of treatment. Different growth trends can result from different amount of CSCs present at the end of treatment in SBRT and CFRT.

Many dynamics of CSCs are neglected in this model for simplification. In breast cancer, Pajonk and colleagues found that radiation can induce progenitor cells to become CSCs. They, also, discovered that fractionated radiation causes more CSCs to be developed [12, 6]. In addition, it has been shown that there are many different types of pancreatic CSCs that have different resistance properties to various types of treatment including chemoresistance. Due to the complex order of pancreatic cancer, a future direction could be to add these various aspects to a model.

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